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DATE: Thursday, February 05, 2004 Printable Copy Create Case

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DB=PGPB,USPT,USOC,EPAB,JPAB,DWPI; PLUR=YES; OP=ADJ			
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L3: Entry 5 of 5 File: USPT Nov 14, 2000

DOCUMENT-IDENTIFIER: US 6146894 A
TITLE: Method for generating hypermutable organisms

Detailed Description Text (20):
Three different transfection schemes were used to evaluate the effects of the PMS2-134 mutation on SH cells. In the first scheme, the expression vectors plus the reporters were co-transfected together. Pools containing greater than 100 clones were generated following selection with hygromycin for 17 days and harvested for Western blot and .beta.-galactosidase assays. SH cells transduced with PMS2-WT and PMS2-134 synthesized polypeptides of the expected size, as assessed with anti-hPMS2 antibodies on Western blots (FIGS. 2A and 2B). As expected, virtually no P-galactosidase activity was observed in SH cells transfected with the pCAR-OF reporter plus PMS2-NOT (FIG. 2C). However, SH cells transfected with PMS2-134 expressed considerable .beta.-galactosidase activity, significantly more than those transfected with PMS2-WT (FIG. 2C). These results suggested that the truncated polypeptide encoded by the PMS2-134 construct perturbs the endogenous MMR machinery, resulting in deletions or insertions that restored the reading frame. The exact nature of these presumed deletions or insertions could not be assessed, as multiple copies of the reporter constructs were transduced under our conditions, and the wild type .beta.-galactosidase sequence was in great excess over the expected mutants, precluding their demonstration by direct sequencing.

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L3: Entry 2 of 5 File: PGPB Sep 12, 2002

DOCUMENT-IDENTIFIER: US 20020128460 A1
TITLE: Method for generating hypermutable plants

Detail Description Paragraph:
[0063] To demonstrate that putative plant MMR proteins are truly involved in MMR biochemical process, cDNAs are cloned into constitutive (31, 32) or inducible (33) bacterial expression vectors for functional studies. Various deletion mutants are generated to produce dominant negative MMR genes. Dominant negative alleles that are identified in the bacterial system are then useful for plant studies. Dominant negative MMR genes are prepared by over-expression of full-length MMR genes or by deletion analysis using standard protocols used by those skilled in the art of molecular biology. One such dominant MMR gene mutant was created by generating a construct with similar domains to that of the human dominant negative PMS2 gene (referred to as PMS134) (13, U.S. Pat. No. 6,146,894). To generate this vector, the ATPMS2 (SEQ ID NO: 4) and hPMS2 cDNA (SEQ ID NO: 3) sequences were aligned and the conserved domain was isolated. FIG. 6 shows a sequence alignment between the human and AT PMS134 cDNAs where a 52% identity is found between the two sequences. At the protein level these domains have a 51% identity (FIG. 7). Dominant negative hPMS134 and ATPMS134 genes were made by PCR and subcloned into bacterial expression vectors. The ATPMS134 was generated by PCR from the cloned cDNA using a sense primer (SEQ ID NO:1) corresponding to the N-terminus and an antisense primer (SEQ ID NO:5) 5' gtcgacttatcacttgtcatcgtcgtccttgtagtcgag- cgtagcaactggctc-3' centered at nt 434 of the ATPMS2 cDNA (SEQ ID NO:4). This primer also contains a flag epitope that will allow protein detection followed by two termination codons. PCR products of the expected molecular weight were gel purified and cloned into T-tail vectors. Recombinant clones were sequenced to ensure authentic sequences. Inserts were then cloned into the inducible pTAC expression vector, which also contains the Ampicillin resistance gene as a selectable marker. The human PMS134 allele was also cloned into the pTAC expression vector as a positive control. Electrocompetent DH5alpha and DH10b bacterial cells (Life Technologies) were electroporated with empty vector, and the loaded vectors pTACATPMS134 and pTAChPMS134, using an electroporator (BioRAd) following the manufacturer's protocol. Bacterial cultures were then plated on to LB agar plates containing 100 .mu.g/ml ampicillin and grown at 37.degree. C. for 14 hours. Ten recombinant clones were then isolated and grown in 5 mls of LB broth containing 50 .mu.g/ml ampicillin plus 50 .mu.M IPTG for 18 hr at 37.degree. C. One hundred microliters were then collected, spun down, and directly lysed in 2.times. SDS buffer for western blot analysis. For western analysis, equal number of cells were lysed directly in 2.times. SDS buffer (60 mM Tris, pH 6.8, 2% SDS, 10% glycerol, 0.1 M 2-mercaptoethanol, 0.001% bromophenol blue) and boiled for 5 minutes. Lysate proteins are separated by electrophoresis on 4-12% NuPAGE gels (Novex). Gels are electroblotted onto Immobilon-P (Millipore) in 48 mM Tris base, 40 mM glycine, 0.0375% SDS, 20% methanol and blocked overnight at 4.degree. C. in Tris-buffered saline plus 0.05% Tween-20 and 5% condensed milk. Filters are probed with a polyclonal antibody generated against MMR polypeptide sequence or a fused tag (e.g. FLAG, HIS, etc.) and a horseradish peroxidase conjugated secondary antibody, using chemiluminescence for detection (Pierce). FIG. 8 shows a western blot of a clone that expresses the human PMS134 protein (FIG. 8A, lane 2) using a human PMS2-specific antibody (directed to residues 2-20) of the hPMS134 sequence (see FIG. 1, and SEQ ID NO:6) or the Arabidopsis PMS134 protein (FIG. 8B, lane 2) using an anti-FLAG antibody directed to the fusion residues at

the C-terminus of the protein. Cells expressing empty vector had no detectable expression.

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L3: Entry 1 of 5 File: PGPB Jul 31, 2003

DOCUMENT-IDENTIFIER: US 20030143682 A1
TITLE: Antibodies and methods for generating genetically altered antibodies with high affinity

Summary of Invention Paragraph:
[0012] The invention also provides methods of making hypermutable antibody producing cells by introducing a dominant negative mismatch repair (MMR) gene such as PMS2 (preferably human PMS2), MLH1, PMS1, MSH2, or MSH2 into cells that are capable of producing antibodies. The dominant negative allele of a mismatch repair gene may be a truncation mutation of a mismatch repair gene (preferably a truncation mutation at codon 134, or a thymidine at nucleotide 424 of wild-type PMS2). The invention also provides methods in which mismatch repair gene activity is suppressed. This may be accomplished, for example, using antisense molecules directed against the mismatch repair gene or transcripts.

Detail Description Paragraph:
[0091] To demonstrate the ability to create MMR defective hybridomas using dominant negative alleles of MMR genes, we first transfected a mouse hybridoma cell line that is known to produce an antibody directed against the human IgE protein with an expression vector containing the human PMS2 (cell line referred to as HBPMS2), the previously published dominant negative PMS2 mutant referred herein as PMS 134 (cell line referred to as HB134), or with no insert (cell line referred to as HBvec). The results showed that the PMS134 mutant could indeed exert a robust dominant negative effect, resulting in biochemical and genetic manifestations of MMR deficiency. Unexpected was the finding that the full length PMS2 also resulted in a lower MMR activity while no effect was seen in cells containing the empty vector. A brief description of the methods is provided below.

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L3: Entry 1 of 5 File: PGPB Jul 31, 2003

PGPUB-DOCUMENT-NUMBER: 20030143682
PGPUB-FILING-TYPE: new
DOCUMENT-IDENTIFIER: US 20030143682 A1

TITLE: Antibodies and methods for generating genetically altered antibodies with high affinity

PUBLICATION-DATE: July 31, 2003

US-CL-CURRENT: 435/69.1; 435/320.1, 435/326, 530/387.1, 536/23.53

APPL-NO: 10/ 243130 [PALM]
DATE FILED: September 13, 2002

RELATED-US-APPL-DATA:
Application 10/243130 is a continuation-in-part-of US application 09/707468, filed November 7, 2000, PENDING

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of U.S. Ser. No. 09/707,468, filed Nov. 7, 2000, the disclosure of which is hereby incorporated by reference in its entirety.